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# ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE
DISEASES OF INFANTS AND CHILDREN
JOHN FITCH LANDON, M.D., Editor

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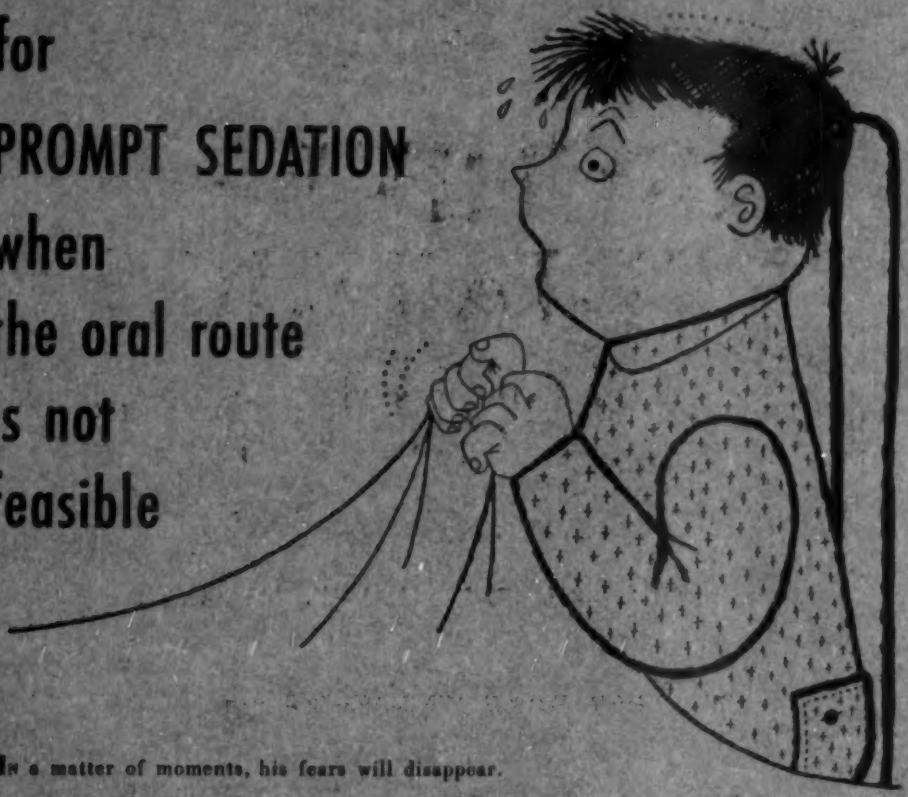

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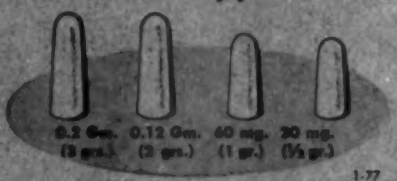


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**REFERENCES**

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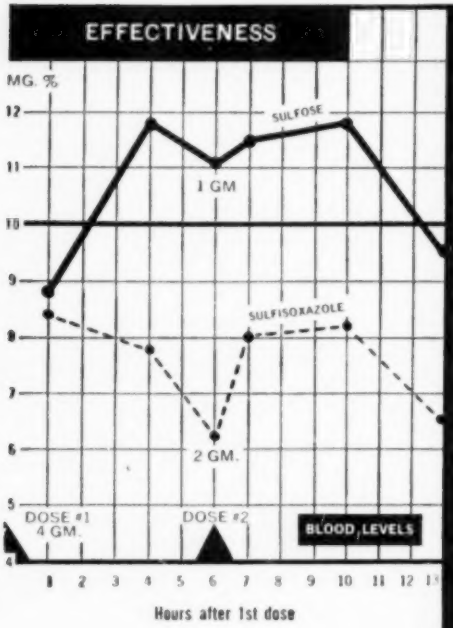


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## STILL'S SYNDROME*

### ATYPICAL JUVENILE RHEUMATOID ARTHRITIS


DAVID H. SPODICK, M.D.

West Hartford, Conn.


The "collagen group" diseases have recently been the subject of increasing interest. In addition to the major entities of this category, many gradations and variants have been identified. One of these, Still's syndrome, has hitherto received comparatively little attention.

In 1897, G. F. Still[47] described a form of chronic rheumatoid disease in children characterized chiefly by polyarthritis, lymphadenopathy and splenomegaly. Prior to this report the occurrence of rheumatoid arthritis in children was well-known. Virchow wrote of juvenile "arthritis deformans" and Charcot speculated on its relation to rheumatic fever as early as 1881[17, 45]. However, the earlier investigators apparently did not recognize the atypical variant described by Still. For more than fifty years this entity has been known as Still's disease—more correctly, Still's syndrome[46].

It is the purpose of this communication to more clearly define this syndrome in the light of a discussion of its clinical peculiarities and associated features. The following case, closely followed for five years before the "cortisone era," is illustrative of the clinical evolution of Still's syndrome.

*Case Report. First Admission:* C. McL., a nineteen months old white male, was first admitted to the Boston Floating Hospital with chief complaint of tender swelling of hands and feet of five


*From the Boston Floating Hospital and the Department of Pediatrics of the Tufts College Medical School.

days' duration following onset of cough and fever. Past history was essentially non-contributory. Examination revealed a toxic, malnourished, dyspneic child. There were scattered rhonchi over both lung fields, tachycardia and a soft apical systolic murmur. The skin exhibited a generalized macular, erythematous rash. There was edema of both hand and feet with ankle and wrist joint tenderness. The liver edge was one finger below the costal margin and there was generalized lymphadenopathy. The spleen gradually enlarged to the umbilicus. On symptomatic and supportive treatment the respiratory symptoms improved rapidly, while the joint swellings and tenderness persisted. Temperature spiked daily between 97° and 105°F. The course was marked by remissions and exacerbations, joint symptoms, temperature, splenomegaly and lymphadenopathy tending to progress or regress together. Laboratory studies showed marked secondary anemia and an initial white cell count of 20,000 which came down to 12,000. Remissions gradually became more prolonged and the splenomegaly receded. Patient was well enough to be discharged on March 29, 1939—83rd hospital day.

*Second Admission:* Patient was readmitted on April 11, 1939 because of recurrent joint swelling. The knees were markedly swollen, and the ankles, wrists and proximal interphalangeals somewhat less so, with tenderness to touch and to active and passive motion; the neck was painful on motion. There was marked generalized lymphadenopathy, the spleen could be felt half way to the umbilicus, and the liver edge was palpated at the umbilicus. The course during this admission varied somewhat from the previous. The temperature was slightly elevated with occasional spikes to 103°F. After the fourth week, the patient had only occasional fever, accompanied by transient articular exacerbations. There was gradual improvement with decrease in joint swellings and shrinkage of nodes, spleen and liver in spite of an intercurrent acute rhinitis and otitis media. Adenotonsillectomy in the thirteenth week had no effect on the general condition. Blood cultures and agglutinations were negative. Patient was discharged on July 24, 1939—104th hospital day.

*Third Admission:* Readmitted December 29, 1939 for recurrent joint pain and swelling of three weeks' duration, involving ankles, knees, hands and right elbow in that order. The patient

appeared acutely ill and had a generalized purpuric macular rash. There was generalized lymph node enlargement, firm, discrete and non-tender. The spleen was two fingers down and the liver almost reached the umbilicus. Oropharyngeal examination revealed a red throat with postnasal discharge. The upper respiratory infection and rash cleared but liver and spleen remained palpable. A short diastolic murmur at the apex was heard and a diagnosis of rheumatic fever superimposed on Still's disease was entertained. Repeated bacteriological studies of blood and joint fluid were negative; stool cultures were essentially negative; hemolytic streptococci grew from nasopharyngeal cultures. Blood chemistries were always normal. The A-G ratio was transiently reversed during the febrile and articular exacerbations which marked the course. Patient improved with subsidence of all symptoms by the ninety-ninth hospital day and he was discharged May 13, 1940—138th hospital day.

*Suscquent Admissions:* Patient was hospitalized September 24 to October 20, 1941 for acute appendicitis; appendix was removed without untoward incident. There was a soft apical systolic murmur, with no evidence of diastolic murmur. Knees, ankles and wrists appeared "bulky" but there was no gross deformity or restriction of motion. Readmitted October 20, 1942 for gastroenteritis. There were small, non-tender palpable cervical, axillary and inguinal nodes. Symmetrical bulbous enlargement was noted at knee, ankle, wrist and elbow joints with no swelling, redness or tenderness. The right knee could not be fully extended and audibly "creaked" on passive motion. Because of a harsh apical systolic murmur, x-ray, fluoroscopy and electrocardiogram studies were done; all were within normal limits. Joint x-rays showed fusiform periarticular swellings and bone atrophy. Several of the carpals were ankylosed. Roentgen interpretation was rheumatoid arthritis (Still's disease). Blood calcium was 11.3 mg.%, phosphorus 3.1. Patient was discharged October 26, 1942—7th hospital day. The last (sixth) admission was for acute otitis media, October 19, 1943 (age six and one-half years). Follow-up study showed only cervical adenopathy, with no palpable abdominal organs. Comparison x-ray studies of joints showed persistence of marked bony atrophy and soft tissue swellings, "consistent with rheumatoid arthritis."

*Comment.* The features of this case accord well with the clinical characteristics and evolution of Still's syndrome. The patient developed progressive multi-articular rheumatoid arthritis, notably affecting first several larger joints and later the proximal interphalangeals. With the onset of joint disease there was great enlargement of liver and spleen and marked generalized lymphadenopathy. Nodes, spleen and arthritis all fluctuated in the same direction during the exacerbations and remissions which characterized the course. Generalized rashes, also present, had no constant relation to the intensity of the process. The patient required a total of 325 hospital days (in three separate admissions) for the initial episode and subsequent recrudescences. Following this, three hospitalizations for non-associated complaints revealed stabilization of the joint disease on follow-up study. The major residua were periarticular swelling and bony atrophy. Generalized lymphadenopathy, splenomegaly and hepatomegaly had completely disappeared.

## STILL'S SYNDROME AS A CLINICAL ENTITY

In the half-century since Still's classic paper[47], a number of reports have appeared in the literature dealing with this subject. Many have been careful studies of genuine cases. Others have employed the designation "Still's disease" loosely as a generic term for juvenile rheumatoid arthritis[13, 32, 37] or for cases lacking one or more of the diagnostic essentials[12, 47, 48]. There have been no sizeable reported series of true Still's syndrome (Still himself only discussed two cases with any degree of completeness[47, 48]. Table 1 is a compilation of individual case studies which have appeared since this entity was first recognized; all exhibited the three cardinal signs: rheumatoid arthritis, lymphadenopathy and splenomegaly; the great majority also showed one or more associated features common to Still's syndrome.

*Age of Onset.* In Still's cases the onset was "always before the second dentition"[47]. This may be regarded as characteristic only of the majority of cases. Of those reported (Table 1), onset occurred in twenty-two before age six, in fifteen between six and twelve and in one at seventeen. Still's youngest patient was fifteen months old; no younger case has been reported. (Lo Presti's[29] fifteen month old appeared more like typical rheumatoid arthritis

and Richdorf's[39] six-day-old infant proved to have a septic condition.)

*Sex.* One of the striking features differentiating Still's syndrome from typical juvenile rheumatoid arthritis is its sex incidence. Still[47] stated that this entity was distinguished by a smaller preponderance of females when compared with rheumatoid arthritis, and gave a ratio of 1.5 to one male. Litchfield and Mason[28] consider the incidence higher in males. The ratio for rheumatoid arthritis in all ages has been given as 1.5 to 2:1[34]; in typical juvenile rheumatoid arthritis there is marked female predominance (5:1)[14]. Of the individual reported cases (Table 1), twenty-three were males and only fourteen females (in one, the sex was not stated)[2]. This would tend to bear out the contention of Litchfield and Mason[28] that Still's syndrome is characterized by male preponderance in contrast to typical juvenile rheumatoid arthritis with its very marked female preponderance.

*Arthritis.* Still's syndrome is characterized by chronic progressive arthritis, usually multiple and symmetrical, accompanied by splenomegaly and lymphadenopathy of a distinctive nature. The onset is most often insidious. Joint symptoms invariably appear in one or more of the larger (weight-bearing) joints (in most of the reported cases, ankles or knees). The proximal interphalangeals, in contrast to classical rheumatoid arthritis, are involved relatively late. Marked periarticular swelling, accompanied by slight pain, increasing on forcible motion[2], typify the disease (some investigators term this a "periarthritis")[28]. A typically acute or "hot" joint may rapidly develop. Even in some early cases "creaking" may be produced on motion. Although Still[47] stated that bony grating is always absent, Schlesinger[42] was able to elicit grating in a few cases.

Almost any joint, and, indeed, almost every joint[7, 19] may become involved. Sternoclavicular and costochondral articulations are occasionally affected[24, 37]. Temporomandibular arthritis, often with resultant distressing nutritional problems, has been reported[20, 24, 37, 40].

*Lymphadenopathy* of a special kind is a distinguishing feature of Still's syndrome[16]. It has the following important features: (1) Regional nodes of affected joints are primarily and most prominently involved; (2) Size of nodes varies directly with exacerbations and remissions; (3) Nodes are firm to hard, discrete,

TABLE 1. *Cases of True Still's Syndrome Reported 1897-1952.*

| No. | AUTHOR | SEX | AGE AT ONSET | JOINTS AFFECTED* | NODES AFFECTED | DEGREE OF SPLENOMEGALY | DEGREE OF HEPATOMEGALY | RBC | Hgb% | WBC | DIFFERENTIAL | COMPLICATIONS-REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Baldwin[4] | F | 5 | Knees, wrists, hips, interphalangeals, cervical spine | Generalized | ++ | | | | | | |
| 2 | Byfield[7] | ? | 4 | "Many joints" | Cervical | + | | | | 25,000 | | |
| 3 | Carroll and Nelson[8] | M | 9 | Ankles, elbows, knees, metacarpals | Cervical | ++++ | ++++ | 2.1 | 40 | 5,700 | P46,L44 | Heart enlarged. Amyloidosis. |
| 4 | Coss and Boots[14] | F | 3 | "Polyarthritis" | Generalized | ++ | ++ | 3.0 | 63 | 30,900 | | Acute yellow atrophy of liver. |
| 5 | Coss and Boots[14] | M | 6 | "Polyarthritis with stiff neck" | Generalized | ++ | ++ | | | 36,000 | | Amyloidosis. |
| 6 | Coss and Boots[14] | M | 8 | "Polyarthritis" | Generalized | ++ | | | | 40,000 | | Generalized rashes. |
| 7 | Edsall[15] | M | 10 | Ankles, knees, left hip, toes, elbows, cervical spine, interphalangeals, metacarpophalangeals, metacarpals, tarsals, wrists, right shoulder | Axillary inguinal, epitrochlear | + | | 6.0 | 60 | 14,000 | | |
| 8 | Finley[18] | M | 5 | Knees | Generalized | + | | 5.0 | 60 | | P37,L29, E16,M15 | |
| 9 | Fitz[19] | F | 4 | "All her joints" | Generalized | ++ | | 3.6 | 60 | 4,700 | | |
| 10 | Hingston[20] | F | 3 | Ankles, elbows, knees, wrists, interphalangeals | Cervical, inguinal, epitrochlear | + | | | | | | |
| 11 | Hingston[20] | F | 2 | Interphalangeals, cervical spine, temporomandibulars, shoulders, hips, knees, ankles, wrists, elbows, toes | Axillary inguinal, Cervical epitrochlear | + | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 12 | Holden[21] | M | 3 | Ankles, knees, hips, metacarpophalangeals, interphalangeals, shoulders, cervical spine, elbows | Axillary, epitrochlear, submaxillary, femoral, inguinal | ++ | ++ | 3.7 | 60 | 18,000 | P50,L40, M9,E0.5 | |
| 13 | Imrie and Aitkenhead[23] | F | 3 | Ankles, knees, elbows, wrists, cervical spine, tarsals, interphalangeals | Axillary, inguinal, cervical | + | | 3.9 | 60 | 25,800 | P78 | Amyloidosis. Erythematous rashes. |
| 14 | Johnston[24] | M | 3 | Ankles, knees, wrists, elbows, interphalangeals, cervical spine | Generalized —esp. axillary, epitrochlear | ++ | | | | | | |
| 15 | Johnston[24] | M | 9 | Ankles, knees, hips, wrists, elbows, cervical spine, interphalangeals, temporomandibular | Generalized | ++++ | | | | | | |
| 16 | Johnston[24] | M | 10 | Ankles, wrists, interphalangeals, hips, temporomandibulars, shoulders, knees, elbows, sterno-claviculars, cervical spine, IV and V costochondrals | Generalized—esp. right epitrochlear | ++ | | | | | | |
| 17 | Langley[25] | M | 4 | Interphalangeals, knees, elbows, metacarpophalangeals, right ankle, wrists | Axillary, cervical, inguinal | + | | 3.6 | 62 | 7,200 | | Pericarditis. Papular rash. |
| 18 | Lindsay[27] | M | 2 | Ankles, wrists, knees, cervical spine | Axillary, inguinal | ++ | | | | | | |
| 19 | Litchfield and Mason[28] | M | 5 | Interphalangeals, elbow, knee, ankle | Axillary, inguinal, cervical | ++ | ++ | 3.5 | 70 | 18,000 | P79,L16, M5 | Maculo-papular rash |
| 20 | Portis[87] | M | 7 | Ankles, knees, cervical spine, wrists, temporomandibular | Axillary, inguinal, cervical, epitrochlear | +++ | +++ | | | 20,000 | | Pericarditis, Myocarditis, aortic, valvulitis, maculo-papular rash |

TABLE 1. *Cases of True Still's Syndrome Reported 1897-1952* (*Continued*)

| No. | AUTHOR | SEX | AGE AT ONSET | JOINTS AFFECTED* | NODES AFFECTED | DEGREE OF SPLENOMEGALY | DEGREE OF HEPATOMEGALY | RBC | Hgb% | WBC | DIFFERENTIAL | COMPLICATIONS-REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 21 | Poynton[38] | M | 4 | Interphalangeals, knees, cervical and dorsal spine, wrists, metacarpophalangeals, metatarsophalangeals | Axillary, inguinal | ++ | +++ | | | | | Left ventricular hypertrophy. |
| 22 | Rosenfeld[40] | F | 5 | Interphalangeals, knees, elbows, hips, ankles, tarsals, "maxillary," cervical and lumbar spine | Cervical, maxillary, epitrochlear, inguinal, axillary | ++++ | ++ | 4.5 | 55 | 13,800 | P62,L29, M7,E2 | Cardiac enlargement. Exophthalmos. |
| 23 | Rossdale[41] | M | 6 | Interphalangeals, wrists, hips, knees, cervical spine, elbows | Axillary, inguinal | + | | 4.8 | 45 | 24,000 | | Pericardial effusion. Recovery following diphetheria. |
| 24 | Schneiderman[43] | M | 4 | Shoulders, elbows, interphalangeals, wrists, knees | Cervical | +++ | | 3.4 | 50 | 22,000 | P65,L36, E1 | Subcutaneous nodules. Elephantiasis of legs. |
| 25 | Sharp[44] | M | 9 | Ankles, wrists | Cervical, retroperitoneal | + | | "Anemic" | | | | |
| 26 | Still[47] | F | 2 | Ankles, elbows, knees, cervical spine, hips, shoulders | Axillary, cervical, epitrochlear, iliac, inguinal | + | | | | | | |
| 27 | Still[48] | F | 7 | Ankles, knees, hips, interphalangeals, cervical spine, elbows, wrists | Axillary, brachial, epitrochlear, iliac | + | | | | | | Cardiac enlargement. |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 28 | Taussig[49] | M | 17 | Elbows, knees | Generalized | + | + | "Anemia" | | 12,250 | "Shift to left" | Pericarditis. Hyperglobulinemia. |
| 29 | Taylor and McKim[50] | F | 7 | Ankles, knees, hips, wrists, elbows, interphalangeals, cervical spine | Cervical, inguinal, axillary, epitrochlear, submaxillary | + | | 5.0 | 87 | 12,000 | P64,M28, E4 | Exophthalmos. |
| 30 | Thursfield[51] | F | 4 | Interphalangealss, knees, wrists, tarso-metatarsals, cervical spine | Axillary, cervical, epitrochlear | ++ | | | | | | |
| 31 | Trasoff, et al[52] | F | 11 | Interphalangeals, wrists, elbows, knees | Cervical | ++ | ++++ | 3.3 | 70 | | | Amyloidosis (Recovered). |
| 32 | Weber[53] | M | 3 | Interphalangeals, knees, elbows, cervical spine | Cervical, axillary, inguinal | +++ | +++ | | | | | Endocarditis, "mitral disease." |
| 33 | Weber[54, 55] | M | 4 | Interphalangeals, knees, elbows, cervical spine, metatarsals, metacarpals | Cervical, axillary, inguinal | +++ | +++ | 4.6 | 31,000 | | | Cardiac enlargement, endocarditis. Improved after jaundice. |
| 34 | Weber[56] | F | 10 | Ankles, wrists, interphalangeals | Axillary, inguinal | ++ | | | | | | |
| 35 | Weber[57] | F | 9 | Wrists, interphalangeals, ankles | Axillary, inguinal | + | | | | | | |
| 36 | Whitman[58] | M | 12 | Knees, hips, elbows, interphalangeals, shoulders, ankles | Axillary, inguinal | + | | "Anemia" | | | "Increased eosinophiles" | Amyloidosis. "Lichen scrophulosum" of skin. |
| 37 | Whitman[58] | M | 4 | Knees, ankles, hips, wrists, elbows | Regional of joints | ++ | ++ | | | | | |
| 38 | Wong[59] | M | 4 | Knees, ankles, wrists, cervical spine, interphalangeals | Axillary, cervical | + | | | | | | Amyloidosis. "Ribbon keratitis" Corneal deposit stained with Congo Red. |

*"Interphalangeals" refers to proximal interphalangeals of the fingers unless otherwise indicated.

non-tender and freely movable; (4) Microscopic examination reveals only non-specific hyperplasia[3, 37, 42, 46, 47]. Presumptive evidence of concomitant enlargement of visceral nodes, at least in some cases, is offered in necropsy studies by Langley[25] and in clinical reports by Holden[21] and Sharp[44].

*Splenomegaly* completes the diagnostic triad. It varies in degree, but is most often pronounced. In Table 1, an arbitrary 1+ to 4+ gradation is employed because of the varying methods of reporting splenomegaly, particularly in the early literature. "1+" may be considered a definitely palpable spleen, just below the left costal margin. Sixteen cases exhibited 1+ splenomegaly, while twenty-two were greater than this (fifteen of 2+, four of 3+ and three of 4+). The degree of splenic enlargement generally parallels that of the lymph nodes.

Anemia is almost invariably present, and, in the great majority of cases, is accompanied by leukocytosis with a normal differential or granulocytic increase[3, 13, 47]. Hemoglobin is usually 60-70 per cent, but readings below 50 per cent are not rare[8, 46]. The red cell count averages three to four million (See Table 1). Sedimentation rates are increased.

Cardiac involvement, usually mild and transient, occurs in a considerable number of cases[8, 25, 47, 49, 54, 55]. Functional murmurs, secondary to anemia, are common. Electrocardiograms show only tachycardia in the absence of pericarditis, pleuritis and endocarditis, which have been reported by a number of investigators[25, 37, 41, 49, 53, 55].

*Associated Findings* mark certain cases: Hepatomegaly (to be discussed) was found in fourteen of thirty-eight cases in Table 1. Mild exophthalmos has occasionally been seen[40, 47, 50]. Various erythematous rashes may be present initially or related to febrile and articular exacerbations but are rarely a clinical problem[40, 46, 47, 50]. Langley[25] states that "to the three cardinal signs may be added in order of frequency: anemia, muscular atrophy, cachexia, pericarditis, pleurisy, exophthalmos and exanthemata."

*Course.* There is general agreement on the self-limited nature of Still's syndrome; a slow course, punctuated by exacerbations and remissions is the rule[11, 13, 36, 42, 46, 47]. The latter gradually predominate and improvement after a maximal period of activity usually supervenes[13]. Whether amelioration is to be complete or partial with stabilization of the process at some intermediate point is not predictable for the individual case. In the latter event, however,

a condition of general joint disease may result. Limitation of motion by contractures followed by fixation in flexion and muscular atrophy represent the fate of the worst of these cases[3, 25, 43, 47]. Ulnar deviation of the wrists, as seen in adult rheumatoid arthritis, was especially noted by Still[47]. Deaths follow complications or intercurrent disease.

### STILL'S SYNDROME WITH HEPATOMEGALY

It is well-known that hepatomegaly as well as splenomegaly may occur in association with Felty's syndrome in adult-type rheumatoid arthritis[16]. Fourteen individual cases of Still's syndrome with liver enlargement are reported in the literature (Table 1). Inasmuch as none of these were reported because of this finding, some idea of the occurrence of hepatomegaly in Still's syndrome may be gained by a comparison of these with the total number of case reports. This yields a crude incidence of 37 per cent. These cases were further individually analyzed to obtain a "corrected" incidence, i.e., to eliminate known associated conditions which could independently result in hepatomegaly. Thus, amyloidosis was present in three[8, 14, 52]; in one, hepatomegaly occurred two years after onset, but it is not clear whether this was actually of cardiac origin[38]. Rejection of these cases results in a corrected incidence of 26 per cent in which liver enlargement was a concomitant of uncomplicated Still's syndrome.

When present, hepatomegaly almost invariably parallels splenomegaly in extent. Thus, with this finding arbitrarily graded on a 1+ to 4+ scale, two cases had marked (4+) enlargement, three cases minimal (1+) and the remaining nine, intermediate (2 to 3+) grades.

### THE HEART IN STILL'S SYNDROME

Still found clinical evidence of adhesive pericarditis in two of his cases; three others exhibited this finding at autopsy[47], and it has been reported elsewhere[11, 37]. Four cases in Table 1 had demonstrable pericarditis. Detectable cardiac enlargement has been described by a number of investigators[8, 38, 40, 48, 54], and evidence of "myocarditis" by one[37], but these findings have usually been transient and related to acute exacerbations.

Endocarditis is rare in genuine Still's syndrome, but its occurrence in a few cases has been noted. Still found slight thickening

of a mitral valve at autopsy but did not consider it significant[47]. Poynton's[38] case had "obvious valvular disease" eight months after the occurrence of typical Still's syndrome and Portis[37] found subacute aortic valvulitis at autopsy. Weber's[53] patient had clinical mitral disease one year after onset.

### AMYLOIDOSIS IN STILL'S SYNDROME

Secondary amyloidosis may occur in the course of tuberculosis, multiple myeloma and chronic suppurative diseases. Occasionally, and in the absence of such conditions, amyloidosis may enter as a serious (almost invariably fatal) complication of Still's syndrome. Generalized or local (hepatic, renal, splenic) amyloid disease may occur; it has even been reported in a submaxillary gland[13]. Still's cases were apparently free of this condition, the earliest described case being that of Whitman[58] in 1903. Carroll and Nelson[8] report a patient in which hepatic deposition of amyloid resulted in a liver weight of 4.3 kilograms (1/18 the patient's body weight). A total of six individual cases has been reported (Table 1), though others have mentioned its occurrence[11, 37].

With one exception, every case of Still's syndrome in which the diagnosis of amyloidosis has been established eventually proved fatal. Trasoff, Schneeberg and Scarf[52] report the only case of recovery. Interestingly, this patient's arthritis persisted despite regression of amyloidosis. In all cases reported, the Congo red test was positive, when used.

Because of the occurrence of amyloidosis, marked hyperglobulinemia should be regarded with suspicion[49, 52]; albuminuria (usually insignificant in afebrile periods) should be similarly regarded. Contrary to one assertion[46], hepatomegaly is not always a reliable guide in raising the question of intercurrent amyloid disease. Of the reported cases, half had no hepatic (and only moderate splenic) enlargement; the remainder had moderately to markedly enlarged livers and proportionately enlarged spleens.

### HYPERGLOBULINEMIA IN STILL'S SYNDROME

Trasoff and his group[52] and Taussig[49] have investigated the level of serum globulin in Still's syndrome. These authors found definite hyperglobulinemia in the cases studied. Taussig's two patients each showed relative and absolute increase in serum globulin, most

marked in the euglobulin fraction. Trasoff's case (with amyloidosis) had transient reversal of the A-G ratio with relative hyperglobulinemia. While these reports are of more than passing interest, characteristic alteration in serum protein cannot be accepted as a constant feature of Still's syndrome (or even a frequent feature) because of the paucity of case material on which these studies have been reported.

### RIBBON KERATITIS AND IRIDOCYCLITIS IN STILL'S SYNDROME

In typical rheumatoid arthritis of both adults and children the occasional occurrence of ocular involvement is a well-known phenomenon. Parsons and Duke-Elder[33] and Holm[22], among others, have described iridocyclitis and band-shaped corneal opacities ("ribbon keratitis") in these patients. Twelve cases have been described with ribbon keratitis as the major finding, all of which had some previous history of arthritic manifestations[23]. Wong[59] discussed twenty-three such cases and presented one of genuine Still's syndrome with iridocyclitis and multiple corneal opacities which eventually coalesced into the ribbon pattern (Table 1, No. 38). This patient also had amyloidosis, with a strongly positive Congo red test, and, strikingly, the corneal deposit stained faintly following injection of the dye.

### SKELETAL CHANGES AND RESIDUA OF STILL'S SYNDROME

General arrest in physical development is the rule in full-blown cases; the mental powers are unhampered[47]. In addition to general bodily retardation, a peculiar bird-like facies frequently develops[14, 47].

Contrary to Atkinson's[3] assertion of the absence of pathognomic changes, several investigators have drawn attention to certain characteristics of the disease. Schlesinger[42] described what he felt were mixed features of hypertrophic and rheumatoid arthritis which occurred in many cases, viz., cartilage destruction, "drilled-out" areas, general bony rarefaction, premature ossification and diaphyseal overgrowth. In a group of 56 cases of juvenile rheumatoid arthritis (60 per cent with generalized lymphadenopathy and 30 per cent with splenomegaly), Coss and Boots[14] observed the frequent occurrence of three changes which also occur in Still's syndrome: (1) Brachygnathia (probably accounting for the bird-

like facies), (2) brachydactyly and (3) cervical fusion. Although Still[37] held that bony lipping and osteophyte formation were characteristically absent, their occurrence has been reported[12]. Generally speaking, skeletal residua are more pronounced with lower age of onset, especially before the sixth year[47].

Metabolic studies by Levin[26] indicate that in spite of general skeletal decalcification there is no derangement of calcium balance.

### INVOLVEMENT OF THE CERVICAL SPINE

Cervical arthritis may be said to be almost a characteristic of Still's syndrome[46]. Still stated that there was "very early and almost constant affection of the cervical spine"[47]. Schlesinger[42] found the cervical spine involved in this form of arthritis more often than in any other and Portis[37] has also called attention to its frequency. In Table 1, at least twenty-one cases had cervical arthritis, 55 per cent of those reported. By contrast, there was only one case each of lumbar and thoracic spine involvement and each of these also developed cervical arthritis[38, 40].

### THE HEMOGRAM IN STILL'S SYNDROME

The changes in the red cell count and hemoglobin have already been discussed. From the data in Table 1 it is clear that this secondary anemia may be normo- or microcytic and normo- or hypochromic. The erythrocyte sedimentation rate is correspondingly increased, excepting during acute exacerbations, when activation of the disease process results in a superadded increase.

The total white cell count is not only raised in most cases, but the degree to which this occurs constitutes an important prognostic sign[46]. Coss[13] states that if the usual tendency to slight increase is replaced by marked leukocytosis, the prognosis is poor. Portis[37], Imrie and Aitkenhead[23], Coss and Boots[14] and Schneiderman[43] all report fatal cases with counts in excess of 20,000. While of distinct aid in prognosis, this finding is not an infallible indicator of the outcome in any given case; a fatal case with no leukocytosis[8] and recoveries with marked white cell elevation[41, 54, 55] have been described.

A characteristic alteration of the differential count is frequently seen in Still's syndrome. Atkinson[3] holds that an increase in neutrophile polymorphonuclears distinguishes Still's syndrome

from "other chronic (lymphocytic) juvenile rheumatism." This statement gains support from eight authors reporting the differential count for individual cases (Table 1), giving polymorphonuclear percentages from thirty-seven to seventy-nine (average sixty per cent); in each case, when multiplied by the total count, the results showed marked polymorphonucleosis; in each, the relative number always exceeded the lymphocytes.

Eosinophilia of significant proportions has also been described. The earliest report (103) is that of Whitman[58]. The most striking instance was Finley's patient with a 16 per cent count[18]. Taylor and McKim[50] report a case with 4 per cent eosinophiles (in a total of 12,000 white cells) and Coss and Boots[14] refer to a case with a count in excess of 5 per cent. The significance of eosinophilia in Stills' syndrome is problematical, but it may well be on a par with its occurrence in other collagen group diseases.

### CLINICAL AMELIORATION FOLLOWING INTERCURRENT DISEASE

Improvement in typical rheumatoid arthritis following the intervention of jaundice, pregnancy and other conditions is a well-known phenomenon. Still's syndrome has been known to act similarly. Still[47] himself observed marked remissions following scarlet fever, "catarrhal" jaundice and measles. Fitz[19] reports a case in which signs and symptoms regressed for one and one-half years following diphtheria. In a case discussed by Rossdale[41], diphtheria was followed by recovery; this same author also reports recovery after "enteric fever." Weber[54, 55], like Still, observed improvement with jaundice. Since, as has been pointed out, there is general agreement on the self-limiting nature of Still's syndrome, to credit amelioration or recovery to intercurrent disease is difficult for any given case ("post hoc ergo propter hoc" reasoning). However, it may be stated generally that certain relatively benign illnesses may favorably alter the course of Still's syndrome.

### THE PROBLEM OF DIFFERENTIAL DIAGNOSIS

That the differential diagnosis of Still's syndrome may offer considerable difficulty is illustrated by a case reported from Cuba by Castellanos and Galan[9]. Diagnosis of Still's syndrome was entertained for a six-year-old whose major findings were polyarthritis, splenomegaly, generalized lymphadenopathy, fever and maculo-

erythematous rash. Post-mortem examination revealed concurrent sarcoidosis and tuberculosis.

It is manifest that those characteristics of Still's syndrome regularly accompanying the arthritis—splenomegaly, lymphadenopathy—and those frequently present, e.g., hepatomegaly and rashes, widen the scope of differential diagnosis beyond typical rheumatoid arthritis and simple arthritic states. Furthermore, the case cited above should emphasize that the very nature of Still's syndrome makes it ideal for confusion with the simultaneous occurrence of more than one disease process.

The following conditions should be ruled out in making the diagnosis: Specific arthritides (especially with generalized disease), other collagen diseases, tuberculosis, infectious mononucleosis, bacterial endocarditis, rickets, meningitis, syphilis, brucellosis, acute exanthematous diseases and the lymphomas and allied conditions.

## NOSOLOGY OF STILL'S SYNDROME

Valid objections to a separate status for Felty's syndrome[16] have been raised by Bauer and others[10]. Classification of Still's syndrome has similarly been the subject of considerable controversy. In considering the related arguments, the problem may be formulated as follows: Does Still's syndrome deserve nosologic distinction from "classic" juvenile rheumatoid arthritis? The weight of evidence would appear to favor a qualified affirmative in answering this question.

Apart from the few unsubstantiated (mostly very early) reports of focal infectious[8, 40] and of tuberculous[15, 57] etiology, three definite schools of thought exist with regard to the nature of Still's syndrome. Coss[13], Burdick[6] and Coss and Boots[14] object to a separate terminology and prefer "rheumatoid arthritis, juvenile type." They feel that Still's syndrome is the same as adult rheumatoid arthritis with clinical differences based on the age group involved. In spite of his statement that the usual roentgen picture "could almost be described as pathognomonic," Schlesinger[42] is in agreement with these authors. It is clear that use of the terminology favored by this group would necessitate classifying other instances of rheumatoid arthritis in young children (the majority of cases) with the "adult" type; this would tend to invalidate the argument that clinical differences of Still's syndrome are based on age group.

In direct opposition are those who consider Still's syndrome a separate disease. Byfield[7] held that Still "was not dealing with rheumatoid arthritis which also occurred in childhood and which resembled the rheumatoid arthritis of adults." He considered Still's syndrome "a joint disease of a special type." Johnston[24], Holden[21] and Parkes Weber[56] are in general agreement with this statement. More recently, Portis[37] concluded that the clinical course and pathology mark this as a "definite disease entity."

Between these extremes is the concept that Still's syndrome, while a definite clinical entity, remains a variant of rheumatoid arthritis. Barker[5] states that "there are sufficient associated findings . . . to separate it somewhat from the other forms." Such separation (from rheumatoid arthritis) is concurred in by Atkinson[3], Angevine[1] and Litchfield and Mason[28]. McCrae[30, 31] classifies it as a "distinct form of arthritis deformans in children." Finally, Ashmun[2] and also Taussig[49], point out the usefulness of a separate terminology to denote this "rather definite" group of cases.

The author is convinced that a separate status for Still's syndrome is justified. Splenomegaly, lymphadenopathy, early affection of weight-bearing joints, tendency to granulocytosis, and marked relative predilection for males distinguish Still's syndrome from typical juvenile rheumatoid arthritis. However, joint affection, the salient feature of the disease process, is rheumatoid in character and this fact cannot be disregarded. Hence, the designation "Still's syndrome" was proposed by me[46] to avoid the nosologic implications of the word "disease." To meet the objections to eponymous terminology, "atypical juvenile rheumatoid arthritis" is included in the title of this communication. Until a more descriptive term is evolved, however, it is suggested that "Still's syndrome" represents the best designation for this entity.

## SUMMARY

A variant of rheumatoid arthritis in children, Still's syndrome is distinguished chiefly by splenomegaly and lymphadenopathy; other features, e.g., hepatomegaly, may be prominent but are not constant. An illustrative case is discussed. The literature is reviewed and case reports tabulated to demonstrate the clinical features and differential diagnosis. The leading opinions on nosology are

presented. It is concluded that the characteristics of Still's syndrome entitle it to distinction from other forms of rheumatoid arthritis.

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CORTICOTROPIN AND CORTISONE IN CELIAC DISEASE. (Schweizerische medizinische Wochenschrift, Basal, 82: 420, April 12, 1952.) The four children with celiac disease whose cases are reported in this paper were boys between 15 months and 5½ years of age. They had had symptoms of celiac disease for from six months to three years. The response to dietetic treatment had been unsatisfactory. Treatment with corticotropin and cortisone was continued for from four to seven weeks, during which a modified dietetic treatment was continued. Corticotropin was given for two days in large doses, then for several weeks in an adjusted maintenance dose and finally in slowly decreasing doses. Patients who were treated with cortisone were given some corticotropin at the end of the course of cortisone. Treatment with corticotropin or cortisone effected improvement in the general condition, mood, appetite, appearance and fat content of stools, sideropenia, anemia, hypoproteinemia, and the blood sugar tolerance tests, but no effect was noted on osteoporosis, on the retarded development of the epiphyseal nucleus, or on the roentgenologically demonstrable changes in the small intestine.—*Journal A.M.A.*

# LEAD POISONING AS A CAUSE OF THE ATHETOID TYPE OF CEREBRAL PALSY*

REPORT OF CASE

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Lead poisoning as a cause of cerebral palsy is extremely rare. In a study of 1,000 cerebral palsy cases, only one such case has been encountered which will be discussed. No case of pure athetosis has been reported formerly.

Lead poisoning has been mentioned as the cause of the spastic type of cerebral palsy by Perlstein[1]. In a review of the literature, lead poisioning has never been discussed formally as a cause of pure athetosis. Byers and Lord[2], in a study on mental development following lead poisoning, list as criteria, evidence of spasticity and choreiform movements. The latter may have been true athetosis. McKhann[3] and Givan[4] have stated that they have never seen pure athetosis caused by lead poisoning.

REPORT OF CASE

D. C., a five-year-old colored girl, was first seen in November 1948. She developed normally, both mentally and physically, until the age of 18 months.

The birth history of the child was normal. She was the first child, weighing 7 pounds 5 ounces, of an 18-year-old mother and was a head presentation, at term, following an uneventful labor.

The developmental history of the child was normal, in that she sat up at 6 months and walked at 13 months. She began talking at 18 months. She developed a tendency to pica when she would put such things as the paint from baseboards and walls into her mouth. Beginning at this age she began to have an unsteady gait, stopped talking and became irritable. She had stopped paying attention when spoken to and there was a noticeable regression in her toilet habits without any known psychological reason. Three weeks before the first examination by one of us (A. D. S.), the child began to have projectile vomiting and became anorexic.

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Physical examination in November 1948, by A. D. S., revealed a well-developed and well-nourished child continually crying and uncooperative. She did not appear acutely ill.

Laboratory data revealed some interesting findings. The child's blood count was not normal in that the hemoglobin was 8.5 Gms. and there were 3.64 million red cells. Differential studies showed 11,400 white blood cells, of which there were 58 polymorphonuclear leukocytes, 26 lymphocytes and 16 eosinophils, also 3 nucleated red blood cells were noted. There was evidence of achromia, anisocytosis, polychromasia and a few stippled red cells. There was not any active sickling but marked latent sickling was noted. Platlets numbered 480,000. Red blood fragility test showed initial hemolysis .42% comp., .28%. Urinalysis revealed 1.011 specific gravity, acid, a trace of albumin, and a few white blood and epithelial cells. Lead determinations of the urine were .035 mgm. lead per 700 cc. of urine or .05 mgm. lead per 1000 cc. The sedimentation rate was 8 mm. per hour.

X-rays of the skull were normal. Numerous x-ray studies revealed the following: (1) Lead lines at the knees and wrists, (2) On an abdominal plate, radiopaque material of metallic density present in the rectum with lead lines in the iliac crest, (3) Essentially a negative abdomen, (4) Chest plate revealed generalized sclerosis of all the bones visible in the film, and in the metaphyses and zones of growth; and also in the chest plate there were deep bands of increased density which are characteristic of lead poisoning demonstrated in the angles of the scapulae and also in the sternal ends of the ribs.

The child at this time was placed on vitamin D and calcium lactate as treatment for keeping the lead in the bones, to avoid further poisoning.

The child was again seen in December 1949 by A. D. S. after a history of several convulsions associated with fever. The examination at this time did not show any change in the child's underlying condition. The gait remained the same.

The child was seen again in May 1950 by both of us. Her general appearance was that of a quiet, cooperative little girl. Her nutrition was good. She walked with a marked limp. On examination, the child's deep reflexes were normal. Careful observation revealed slow involuntary rotary motions in the feet, forearms and hands. There were no other significant positive findings. A diag-

nosis of rotary athetoid type of cerebral palsy was made. At this time, because of some success in using artane in postencephalitic athetoids, the drug was advised. It was not used until April 1951 because the parents delayed in obtaining the drug.

In June 1951, the child was again examined by R. V. M. The involuntary motion had become minimal but she still walked with a limp though much decreased. Some speech had returned. The child appeared more alert and there was improvement in her toilet habits.

SUMMARY

Lead poisoning as a cause of cerebral palsy is known but has never been reported heretofore as a cause of pure athetosis. Whether or not artane is effective cannot be judged by a single case.

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EYE CHANGES IN CONGENITAL HEART DISEASE. (Klin. Monatsbl. für Augenheilkunde, Stuttgart, 120: 351, 1952). Ophthalmologic studies were made on 74 patients with congenital cardiac defects, at a time when the exact nature of the defect had not as yet been ascertained. Later it was found that 27 had the tetralogy of Fallot, 15 had Eisenmenger's complex, 11 had patent ductus arteriosus, and 21 had various atypical deformities. The children with patent ductus arteriosus without cyanosis, also had no eye ground changes or polycythemia. However, children with the tetralogy of Fallot or symptoms of congenital cyanotic heart disease had eye changes such as cyanosis of the conjunctivas and retinas, erythema of the optic papillae, tortuosity, and dilatation and darkening of the retinal vessels, particularly of the veins. The degree of eyeground changes corresponded to the severity of the cyanosis and polycythemia. They are regarded as manifestations of compensation. The chronic oxygen deficiency characteristic of this form of heart disease is present also in persons at high altitude, and similar changes are observed in their eyes before acclimatization has taken place.—*Journal A.M.A.*

# CLINICAL REVIEW

*In order to encourage the writing of clinical articles by recent graduates or senior medical students, the* ARCHIVES *will publish monthly at least one such paper from the classes of Doctor Reuel A. Benson, New York Medical College, New York, and Doctor Philip Moen Stimson, Cornell Medical School, New York. Other interested medical schools are cordially invited to submit student papers for consideration.*

## THE INTEGRATION OF MICROMETHODS OF BLOOD ANALYSIS INTO PEDIATRIC PRACTICE*

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It must readily be admitted that large inroads into the constantly shifting interface between the known and unknown have been made in recent years as a direct result of the application of the laws and methods of the pure sciences to clinical research in all branches of medicine. This trend has resulted in the addition of a tremendous body of knowledge concerning the nature and treatment of disease to the medical literature. Nevertheless, a wide gap exists between such available knowledge and methodology and its actual clinical application in the acute general hospital. The blame for this state of affairs does not lie with any one group of individuals, but rather it should be placed upon the great rapidty with which the entire field of laboratory medicine developed. Each analytical procedure which we know today was developed in a well-equipped and well-endowed institution as a major research project. Macromethods were thus worked out by the monumental efforts of Folin, Wu and others, and they have certainly served a useful purpose for many years now. One of the purposes which they served is the accumulation of a wealth of material as to normal values of various body constituents in both health and disease. In addition, they have also served as the basis for the development of a number of extremely useful so-called function tests. This very backlog of information has made possible the development of a battery of microprocedures of comparable accuracy.

Thus, the great majority of physicians, technicians and hospitals were just beginning to feel at home with macromethods when microprocedures commenced to appear. Little enthusiasm was

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shown by hospitals and technicians for the adoption of what appeared to be a more complicated system.

Unfortunately, repeated venepunctures are difficult to perform on children in order to procure the large amounts of blood required for presently employed macromethods. In this light it would appear to be especially desirable to integrate pediatric practice with microblood analysis. Micro is axiomatically assumed to mean that the procedure requires a sufficiently small amount of blood to be collected by capillary puncture. Any conversion to micromethods is largely a matter of changing methods of collection of samples for the well-equipped laboratories which most hospitals have today. It behooves all practitioners, especially today, to employ all means at their command to elevate further the standards of medical care and yet remain within economic bounds of reason. One means of accomplishing this purpose is the more widespread use of micromethods. It is the purpose of this paper to illustrate certain economically feasible methods of integrating micromethods into the solution of pediatric laboratory problems.

## THE SAMPLING PROBLEM

The latest edition of Mitchell-Nelson's "Textbook of Pediatrics" discusses the collection of capillary and venous blood. Perusal of this section reveals that there exists no comparison between the two methods. All sites which may be employed for venepuncture require considerable restraint of one type or another. It is quite likely that this restraint does a number of undesirable things to the child. Psychological trauma may be inflicted which might result in the development of a morbid fear of physicians and medical equipment. This is certainly not an ideal state of affairs when the medical profession at large is attempting to persuade adults to present themselves for periodic cancer detection examinations. It also appears that the physiological effects of struggling and the excitement which accompany venepuncture do not materially aid in the promotion of rest and reduction of fever. And, unless precautions are taken, which does not often occur, infectious aerosols are liable to be transferred to the infant by the operator and his assistants because of the close proximity required to accomplish venepuncture. Finally, there exists a small number of cases where many efforts to perform venepuncture result in failure or the collection of an inadequate amount of blood to furnish the required data.

It was formerly stated that the means was justified by the end which was undoubtedly true in a considerable number of cases. However, this argument is no longer valid, since there are available today micromethods of a high degree of accuracy for the determination of all clinically important blood constituents except serum sodium and potassium.

## COLLECTION OF CAPILLARY BLOOD

The proper collection of the specimen is requisite for the production of accurate results in any quantitative determination. The author wishes to set forth his method of capillary puncture which is especially valuable in the newborn. The underlying principles are applicable to any age group.

*Procedure. Multiple Puncture Technique:* The skin overlying the heel of either foot is cleansed thoroughly, using a cotton pledget moistened with a 70 per cent solution of ethyl alcohol. The area is then thoroughly dried, using a second dry cotton pledget which is then discarded. Using a sharp pointed Bard-Parker blade (No. 111) guarded by a cork so that the point protrudes from below the cork for a distance of four millimeters, the skin in an area of not more than four millimeters diameter is rapidly punctured four times. The first drop of blood to appear is then wiped away with another dry cotton pledget. The infant is then allowed to kick the leg for fifteen or thirty seconds until a second drop of blood is seen to appear spontaneously at the wound site. With the aid of gentle squeezing, the required amount of blood is collected into the proper receptacle. The site of puncture is then covered with another dry cotton pledget secured by a small strip of adhesive plaster. The adhesive plaster is removed after twenty-four hours.

Use of this multiple puncture technique produces a wound which might be termed more correctly an arteriolar-venous sinus rather than a capillary puncture. Intravascular pressure is sufficient to propel blood through the sinus tract thus produced, because the wide orifice at the skin surface offers little resistance to a good free flow. Lowry and Hunter[1] have compared serum protein values in capillary blood from the ear and finger with those found in venous blood. They found that even pronounced squeezing did not affect these values significantly after the first drop of blood and all traces of alcohol had been wiped away. The same conclusion may also be reached from a study of the hematocrit values. The

most important single factor is a free flow of blood. Use of the procedure described allows for the free flow and collection of several milliliters of blood from one series of punctures. If it is desired to collect more blood, one further puncture may be made at the same site which will re-establish the flow of blood. Another advantage of this method is that rapid healing ensues since the multiple puncture leaves small islands of epithelial tissue at the wound surface which grow rapidly in all directions. Proper technique will never result in a contused heal or wound infection.

The technique described is advantageous in infants. Within individual limits, it is preferred to use the finger as a site for puncture as soon as that member is sufficiently large. The finger is more desirable because of its high degree of vascularity and the dependency of the hand.

Capillary blood for familiar routine hematological procedures is collected into suitable diluting pipettes or placed upon slides or cover slips for examination of stained smears. Other devices are used for the collection of samples for microchemical analysis, and certain special procedures. The Landau-Adams tube is used for the collection of blood for microsedimentation rate determination. The micro-hemo-pipette of Kato[2] is also commercially available and can be used to determine the sedimentation rate, the hematocrit, and the icterus index. Capillary tubes may be used for the determination of coagulation time, and this subject has been extensively reviewed by DeTakats[3]. The capillary tube of even inside diameter is used in Strumia's method of hematocrit determination. Small serological test tubes containing the appropriate amount of saline are used for the collection of saline suspensions of cells.

An item not available commercially which is of great value is the Wright tube[4]. This device fills by capillarity and may be made in the laboratory in large numbers by any technician. These tubes may be made in varying sizes, one convenient size being 0.5 ml. from which 0.2 ml. of serum may easily be removed. By the use of a slightly larger bore tube and a small increase in length, the capacity may be increased to 1 ml. The tube may be made to contain appropriate amounts of heparin, oxalate, or other anticoagulant when whole blood is required in the fluid state. To take off the serum after centrifugation it is necessary to make suitable capillary tip pipettes out of narrow glass tubing. Any technician

can become adept in the construction and handling of these devices with a little practice.

Economies of large magnitude may be effected by the use of these devices for the collection of capillary blood as compared with the cost of preparation and maintenance of equipment necessary for venepuncture. Valuable technician's time is saved by the simpler procedure too.

One outstanding example of economy is seen in Strumia's[5] capillary tube hematocrit method. Blood is collected by capillary puncture into a capillary tube of uniform inside diameter. The tube is sealed at both ends in the flame and centrifuged for five minutes at approximately 50,000 R.P.M. in an air turbine centrifuge. The respective heights of the plasma and cell columns are measured with a vernier caliper, and the values are converted to the familiar per cent expression by a simple mathematical operation. This procedure has the following advantages: (1) No venepuncture necessary; (2) capillary tubes cost only a fraction as much as Wintrobe tubes; (3) air turbine centrifuge never wears out and has low initial cost; compared with large electrically powered instruments; (4) rapidity reduces the cost of labor. In addition, the vernier reading is extremely accurate and is independent of the absolute volume of the original blood sample. According to Ham and co-workers, the average cost of hematocrit determinations in the U. S. today ranges from $1.00 to $2.00 at the present time. It is felt that these determinations could be done for $0.25 by the Strumia method. Thus, several follow-up determinations could be carried out as necessary in blood replacement therapy, for example, for the price of one of the old macromethod. Considerable savings with improved standards of care are thus passed along to the patient.

These same general principles of economy are seen to operate in many other micro-analytical techniques. King has stated that micromethods, in general, require smaller quantities of costly reagents, less cumbersome methods of collection of samples, and reduced labor cost per unit determination.

Illustrative examples in selected pediatric laboratory problems follow. No attempt is made to give technical details of the procedures mentioned. These are completely indexed in the bibliography. Likewise, no attempt is made to supply interpretative data. The

suggested laboratory tests are mentioned and a summation of the amount and kind of blood to be collected is made. The graphic method of charting is suggested.

### BASIC HEMATOLOGICAL SCREENING

Ham and his co-workers have exhaustively analyzed the value and limitations of the presently employed techniques for the enumeration of the various formed elements of the blood and the determination of hemoglobin. Since these tests may all be performed using capillary blood, it may be stated that they are true micromethods. It must be emphasized that the determination of any one given value is of little value in many cases where such a value may fall within the normal limits for the age group of the child. Far more important is the establishment of a trend. Using these methods employing capillary blood, repeat examinations are easily performed; and it is recommended that their results be tabulated in graphic form similar to a temperature chart. In this way subtle trends will be easily visualized. An example of this might be found in the early establishment of a leukopenic trend in a child who is receiving a drug which is either known to bring on leukopenia, or more important in the evaluation of new drugs whose toxic properties are as yet largely unknown. In addition, it is far easier from a clerical point of view to enter a point on a graph than to paste a report slip on a chart, not to mention the time wasted in thumbing through report slips arranged on a chart in a haphazard manner.

For the sake of completeness, the other examinations necessary in basic screening must be mentioned although they do not fall within the category of micro-analysis of blood. Included is the complete chemical and microscopic analysis of the urine, and basic examination of the stool, serology, and basic blood chemistry analysis. Strumia[6] has recently set forth a guide for the selection of laboratory determinations required in certain clinical problems.

### APPLICATIONS DURING PREMATURITY

Many studies of the physiology of the premature infant are at present under way. Many further studies could be carried out for the surface is still barely touched. Certain groups are experiment-

ing with the use of the umbilical vein as a site for polyethylene tube catheterization for both parenteral alimentation and the withdrawal of blood samples. These studies are interesting from a teleological point of view since it is felt that this situation more closely simulates in utero conditions. However, when one is dealing with an infant whose total blood volume is only three hundred milliliters, the daily or postprandial withdrawal of sufficiently large quantities of blood to perform all of the macromethod analyses which might be necessary in a given functional study could conceivably lead to an anemic situation, unless this blood was replaced by transfusion. This difficulty is obviated to a considerable extent by the use of micromethods requiring only a fraction as much blood as the older macromethods.

It may be mentioned that the simplified technique of intravenous catheterization set forth by Pitesky[7] is recommended for use in older children too where fluid replacement is necessary and where serum sodium and potassium determinations are necessary. The most reliable and accurate method of determining the quantities of these ions present in the serum is by flame photometry which as performed today requires larger amounts of blood than can be conveniently obtained by capillary puncture.

### APPLICATION IN ERYTHROBLASTOSIS FETALIS AND JAUNDICE

Erythroblastosis fetalis, or hemolytic anemia of the new born, is a pediatric problem wherein the laboratory plays a major diagnostic and therapeutic role. Both of these ends are facilitated by the use of micromethods none of which, as it will be seen, are especially new. This laboratory work-up should start during gestation when it is the responsibility of the attending obstetrician to have the mother's and father's major blood group and complete Rh typing determined. If the resulting situation is one in which maternal sensitization might occur, it is wise to observe the maternal blood serum for the presence of antibodies according to the method of Coombs during the last trimester of pregnancy. Whether this is done or not, every child born of a mother who might be sensitized, regardless of prenatal titer determinations, should be subjected to the following complete work-up at birth:

| *Determination* | *Amount & Kind in ml.* |
|---|---|
| Basic hematological screening | 0.2...whole blood diluted properly |
| Micro prothrombin time | 0.05...Micro-hemo pipette |
| Hematocrit | 0.05...capillary tube |
| Major group and complete Rh (CDE) typing and Coombs' test | 0.05...saline tube |
| Sample of serum for icterus index and cross matching of blood | 0.5 ...Wright tube |
| TOTAL AMOUNT OF WHOLE BLOOD | 0.85 |

The above table needs little explanation. This work-up may be completed in approximately one hour where blood banking facilities are available. It is also advisable to determine the hemoglobin concentration hourly so that trends may be established in the progress of the hemolytic progress as a guide to therapy. Repetition of the icterus index is also of value as a follow-up procedure. It is recommended that these values be charted in graphic form.

### DIFFERENTIAL DIAGNOSIS OF JAUNDICE

There are a number of tests available which aid materially in the determination of the etiology of jaundice. The following may be performed using capillary blood, after ruling out erythroblastosis:

| *Determination* | *Amount & Kind in ml.* | |
|---|---|---|
| Basic hematological screening | 0.2 | whole blood diluted |
| Cephalin flocculation | 0.5 | serum from Wright tube |
| Alkaline phosphatase | 0.05 | Lang-Levy pipette |
| Prothrombin time | 0.05 | microhemo pipette |
| Icterus index | 0.05 | microhemo pipette |
| Cholesterol & esters | 0.5 | serum from Wright tube |
| Thymol turbidity | 0.5 | serum from Wright tube |
| TOTAL AMOUNT OF WHOLE BLOOD | 1.85 | |

The information derived from these tests, plus examination of the urine for the presence of bilirubin and urobilinogen, should reveal the nature of the jaundice in the majority of cases. If doubt still remains, the van den Bergh reaction may be resorted to, and a venepuncture done to procure the large amount of serum necessary for the performance of this reaction. Quantitative serum bilirubin determinations likewise require venepuncture for sampling. However, it is felt that the often repeated icterus index serves as an adequate guide as to the amount of bilirubin present in the serum. Studies of fecal bile pigments are also useful.

APPLICATION IN SEVERE INFANT DIARRHEA

It has been recommended that a cut-down procedure be done on admission to obtain venous blood for laboratory work-up and for the administration of parenteral fluid. It is possible to perform all of the indicated laboratory work on capillary blood so that the results are available faster, thus reducing the time wherein therapy is on an empirical basis. The following laboratory determinations are usually considered adequate:

| *Determination* | | *Amount & Kind in ml.* |
|---|---|---|
| Basic hematology | 0.2 | whole blood diluted |
| $CO_2$ determination | 0.1 | serum (0.03) from Wright tube |
| Hematocrit | 0.05 | capillary tube |
| Total plasma protein | 0.5 | Wright tube w heparin |
| Blood type | 0.05 | Saline tube suspension |
| Serum for X-match | 0.5 | Wright tube |
| TOTAL WHOLE BLOOD REQUIRED. | 1.4 | |

The utilization of the method devised by Natelson for microcarbon dioxide determinations makes this regime possible. The high initial cost of this apparatus is well worth while since it also may be used for oxygen, carbon monoxide and nitrogen determinations. Fluid may be administered by clysis subcutaneously thus obviating the need for venepuncture. However, it is considered desirable in severe cases to have a cut-down ready possibly with the use of a polyethylene catheter for the administration of whole blood and the withdrawal of blood samples for serum sodium and potassium determinations[8]. It is not necessary to have information regarding potassium available at once since this salt may not be administered with safety until hydration is sufficiently well along to be accompanied by a return of renal function. The progress of the therapy may be followed by microcarbon dioxide determinations and capillary tube hematocrit determinations usually every six hours until the oral feeding routine is started. It is recommended that these values be plotted on a chart so that early visualization of trends may be accomplished.

APPLICATIONS IN CLINICAL INVESTIGATION OF THE CELIAC SYNDROME IN CHILDREN

An excellent example of the type of physiological investigation

which may be facilitated by the use of micromethods of blood analysis is found in Shohl, May and Schwachman's[9] studies of pancreatic function in the celiac syndrome. These authors were able to demonstrate by means of amino acid nitrogen determinations on the blood of both normal and celiac children in both pre- and post-prandial states that lack of pancreatic trypsin (established by duodenal drainage studies) so inhibits protein digestion in the intestines that absorbable end products are not present in sufficient quantity to provide an adequate protein intake from a diet which had previously been calculated to contain adequate protein for the child's age, height and weight. These determinations were greatly facilitated by the use of the micro-amino acid nitrogen method of Krauel which requires 0.2 ml. of whole blood.

In the accepted treatment of celiac disease today, the phase one diet may be investigated to see if adequate protein is being absorbed by this method. The studies of West, Wilson and Eyles[10] demonstrate the adequacy of various protein diets, according to their effect on the level of blood amino acid nitrogen.

Another micromethod which is of value in the evaluation of mild celiac disease or starch intolerance is Fennel's method for the determination of serum amylase which requires 0.1 ml. of serum for its determination.

### APPLICATION TO RENAL DISEASE AND AZOTEMIA

All instances of renal disease where it is desirable to know the concentration of nitrogenous substances in the blood stream may be well served by the use of micromethods. This is especially so in the performance of urea clearance tests and in the management of nephrosis today. Micro-studies may be repeated often enough to establish reliable trends in the course of renal disease which is characterized by periods of exacerbation and remission. The available methods are listed in the bibliography.

### APPLICATION TO ENDOCRINE AND METABOLIC PROBLEMS

In the diagnosis and management of thyroid problems, especially cretins, capillary blood methods greatly facilitate therapy. Basal metabolic rate is difficult to obtain, and cholesterol determinations have been established as an alternative method of therapeutic evaluation. The method of Schoenheimer and Sperry, using capil-

lary blood, is especially adaptable to the needs of repeated determinations over long periods of time.

The glucose tolerance test, as well as the management of diabetic coma and acidosis in children, is facilitated by the use of the Somoygi micromethod for true sugar which can be done on capillary blood. This method coupled with the rapid $CO_2$ method of Natelson provide adequate information for the management of juvenile diabetic states which are so markedly characterized by rapidly fluctuating changes ascribed to endocrine immaturity.

## DISCUSSION

Consideration of the applications of micromethods which were presented should indicate the large number of venepunctures which children may be spared. It would be impossible to cover all of the instances where micromethods might be advantageously applied in pediatric practice. Suffice it to say, however, that wherever a micromethod, of as good a degree of accuracy as the clinical situation requires, exists, it should be used. The knowledge of the individual physician remains as the sole criteria for the worth of the interpretation of any given determination. However, it is hoped that the more widespread use of micromethods will make more data available for good interpretative effort in pediatric cases where it is often life saving.

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BRONCHOPNEUMONIA DUE TO PERTUSSIS. (Belgisch Tijdschrift voor Geneeskunde, Leuven, 8: 377, April 15, 1952). Beckers stresses that in diagnosis of bronchopneumonia due to pertussis two forms should be differentiated: (1) the pneumowhooping cough of Julien-Marie, which is hematologically characterized by the presence of many leukocytes and lymphocytes; (2) bronchopneumonia of the mixed infection type, with an increase in neutrophils but a less decisive increase in leukocytes. The treatment of these two forms differs: in the so-called pneumowhooping cough, the author recommends administration of a specific antibiotic such as terramycin, aureomycin or streptomycin, inasmuch as there may be a difference in sensitivity of some strains against these specific antibiotics. In the treatment of bronchopneumonia due to mixed infection it is essential to administer besides one of these antibioics also penicillin, which has previously been the drug of choice in treatment of pneumococci and streptococci, chief causes of mixed infections.—*Journal A.M.A.*

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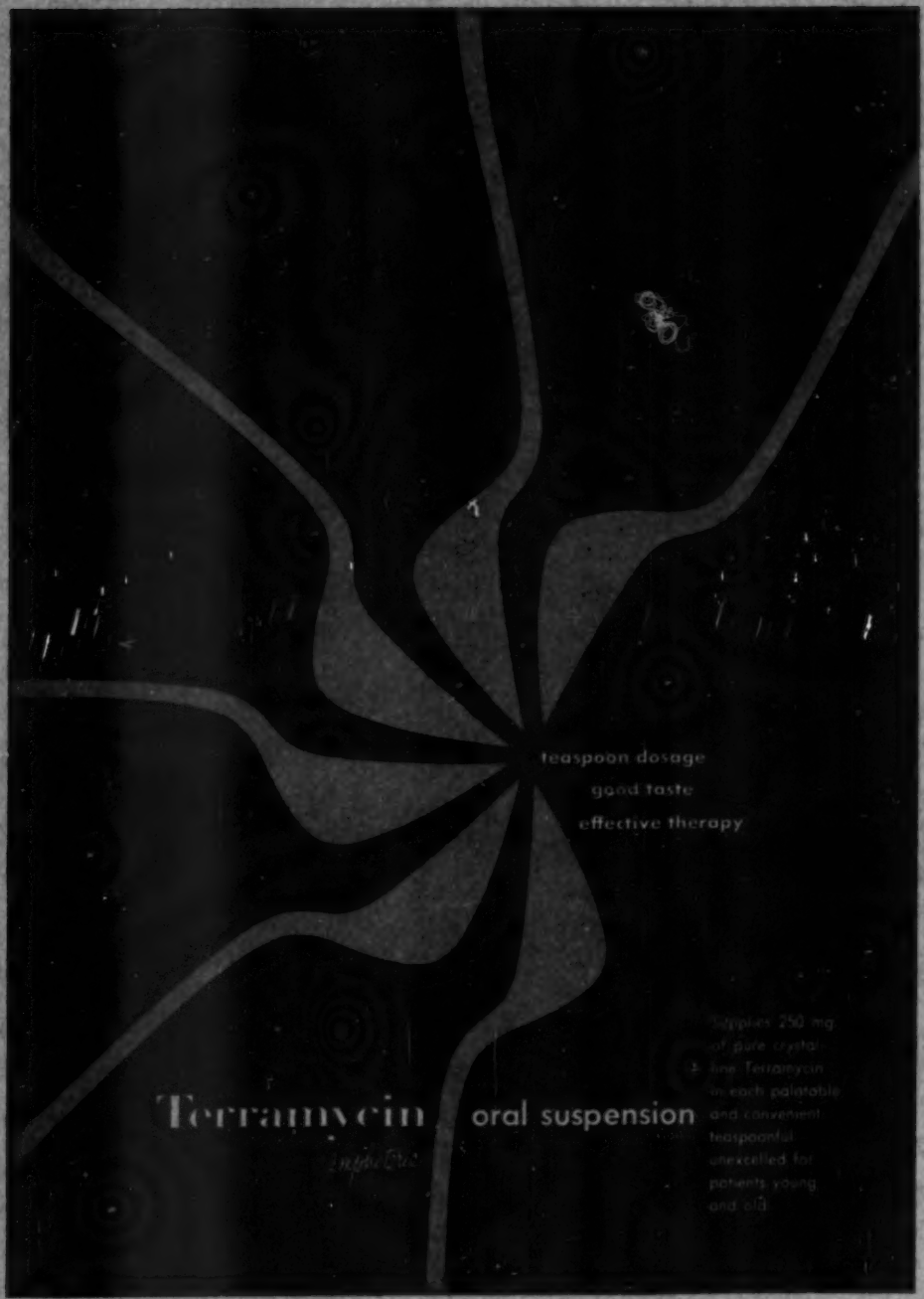
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